The interview among Examiners Anders and Eyler, Henry Einav, who is a representative of the assignee of the present invention, and the undersigned attorney, conducted on January 17,2001, is gratefully acknowledged. In this interview, possible additions to the composition claims in order to amend around the prior art was discussed, as well as language which would clarify "biological activity" of type 1 interferon. No agreements were reached at the interview, but the present amendment and the arguments presented herein are a result of the discussions conducted at the interview.

Claims 10, 11, 15-17, 21 and 24 have been rejected under 35 USC 102(b) as being anticipated by either Cohen (MCB) or Yeda (EPO 588177). The examiner states that the "consisting essentially of" language encompasses the addition of a radioactive iodine atom as this atom would not affect the basic and novel characteristic of binding to IFNAR. The examiner states that the pharmaceutical composition comprising IFNAR2 in the '177 patent anticipates the pharmaceutically acceptable formulation of claims 21 and 24. This rejection is respectfully traversed.

Claim 10 has now been amended to specify that the molecule is isolated. In both Cohen and Yeda, any cross-linked complex of radio-iodinated interferon with IFNAR is never separated from IFNAR or interferon which has not been

cross-linked with one another. In both cases, the interferon and the IFNAR are subjected to cross-linking conditions and then immunoprecipitated, either with anti-IFNAR antibody or anti-interferon antibody. The immunoprecipitate is then run on a protein A-Sepharose column and the bound proteins eluted and analyzed by SDS-PAGE and autoradiography. See the paragraph of Materials and Methods bridging pages 4208 and 4209 in Cohen. A similar procedure was used in Examples 5 and 6 of Yeda in which the anti-interferon antibody was immobilized on agarose hydrazide.

In the situation where an anti-IFN antibody is used, any interferon which is not cross-linked to the IFNAR will also be bound by the antibody and eluted from the column or the beads, and thus will be present with the interferon IFNAR cross-linked complex in the supernatant, which is subsequently subjected to SDS-PAGE and autoradiography. One would not expect to see the non-complexed interferon in the gels of Figure 3 of Cohen, because the smallest size shown on the gel is 45 kD, while interferon has a size of less than 25 kD (see page 2, lines 10-12, of the present specification). Thus, the complex on the gel is not isolated as it is never separated from the gel, and the mixture in the supernatant that is subjected to SDS-PAGE does not contain isolated cross-linked complex as it also contains free interferon.

If an anti-IFNAR antibody is used, any IFNAR which is not cross-linked to the interferon, will be present in the supernatant that is eluted from the column or the beads, and will not show up upon autoradiography as it is not radioiodinated. Furthermore, the supernatant is not isolated cross-linked complex, because it also contains non-cross-linked IFNAR.

Accordingly, even if the term "consisting essentially of" is not interpreted so as to exclude radioiodinated interferon, the claims as amended are not anticipated by either Cohen or Yeda, because neither Cohen nor Yeda show isolated complex. Furthermore, it is still urged that the "consisting essentially of" language does not comprehend radioiodinated interferon, as the definition noted by the examiner on page 32 refers only to additional amino acid residues flanking the interferon binding polypeptide. Such language does not comprehend derivatization of amino acids within the sequence. This is covered by the functional derivative clause of the claim. A molecule consisting essentially of a sequence only includes that non-derivatized sequence with or without flanking residues, which flanking residues do not affect the interferon binding characteristics of the sequence. Just as additional amino acid sequences within the specified core sequence are excluded, so are

derivitizations within that specified core sequence. In either event, claim 10 is no longer anticipated by either Cohen or Yeda. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

As to the pharmaceutically acceptable formulation of claims 21-24, the examiner refers to page 2, lines 3 and 49, page 6, lines 3-16, and page 17, line 7, of Yeda. These passages refer only to pharmaceutical compositions of IFNAR, not of any complex of IFNAR with interferon. Certainly, there is no disclosure whatsoever of a complex of IFNAR with interferon, let alone a cross-linked complex. The only disclosure of a complex of IFN with IFNAR is an incidental disclosure of radioiodinated interferon with IFNAR which cannot be used therapeutically because of its toxicity. Furthermore, such complex is not isolated. Just because a disclosure may dominate a particular pharmaceutical composition, does not anticipate a particularly claimed composition. In order to anticipate, a reference must disclose every feature of the claim. Claims 21 and 24 require a complex of IFNAR and interferon in a pharmaceutical composition. All of these elements are not present in Yeda and, therefore, there can be no anticipation. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

Claims 12-14, 18-20 and 22 have been rejected under 35 USC 102(b) as being anticipated by Yeda. The examiner states that Yeda teaches a pharmaceutical composition comprising IFNAR2, anticipating claim 22, and further teaches pharmaceutical compositions comprising fused proteins, thus anticipating claims 14 and 18-20. This rejection is respectfully traversed.

As discussed hereinabove, in order to be an anticipation, the reference must teach every element of the claim; see MPEP §2131. Claim 12 requires both interferon and IFNAR. Furthermore, it must be isolated. Furthermore, the fusion protein of claim 18 must contain interferon and IFNAR, as does the host cell of claim 19 and the method of claim 20. The mere general disclosure in Yeda that IFNAR may be part of a fusion protein does not anticipate the specific fusion protein of IFNAR with interferon. This is nowhere disclosed in Yeda. In this regard, see MPEP §2131.02 in the subsection entitled

> A GENERIC CHEMICAL FORMULA WILL ANTICIPATE A CLAIMED SPECIES COVERED BY THE FORMULA WHEN THE SPECIES CAN BE "AT ONCE ENVISAGED" FROM THE FORMULA.

This clarifies that, unless the claim species can be at once envisaged from the formula, there is no anticipation even though the formula may cover that species. Here, there is a generic formula of fused protein containing IFNAR. However,

there is no suggestion that it is fused to interferon, and, therefore, the specific IFNAR interferon fused protein cannot be at once envisaged from the formula of Yeda. The same is true with respect to the pharmaceutical composition of claim 22. The mere fact that Yeda teaches a pharmaceutical composition comprising IFNAR2 does not cause one to once envisage a pharmaceutical composition which contains not only IFNAR2, but also interferon. There is no anticipation of this specific pharmaceutical composition from a disclosure only of a composition containing one of the two ingredients of claim 22. For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 10, 11, 15-17, 21, 22 and 24 have been rejected under 35 USC 102(b) as being anticipated by Novick. The examiner states that the incorporation of a radioactive iodine atom is included in the "consisting essentially of" language. This rejection is respectfully traversed.

The Novick reference in the second paragraph of the Materials and Method section on page 713 describes the cross-linking of p40 with ^{125}I-IFN-α2 followed by affinity purification with anti-IFN antibody beads and SDS gel electrophoresis and autoradiography. Thus, this process is exactly the same as those described in Cohen and Yeda insofar as the isolation of the cross-linked complex is concerned.

Claim 10 has been amended to specify that the product is isolated. The product of Novick is not isolated for the same reasons as discussed above with respect to Cohen and Yeda. Furthermore, as to claims 21 and 24, this complex of p40 with radioiodinated interferon is never placed into a pharmaceutically acceptable formulation. Accordingly, none of these claims are anticipated by Novick. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

In the interview, Examiner Eyler requested that we insert a brief explanation in our response why the present compositions are not obvious from the references. A novel composition is not obvious unless the prior art contains some motivation to modify the references in a manner which will result in the claimed composition. There is no motivation to isolate radioiodinated interferon-IFNAR complex as there is no known utility for such a complex. It was only created in order to analyze for the presence of the complex or to prove that the interferon binds to the IFNAR, but there is no suggestion of any utility for a complex of interferon with IFNAR, particularly when the interferon is radioiodinated. Furthermore, there is no suggestion of why one would cross-link non-radioiodinated iodine to IFNAR and then isolate it. This would not have the utility of the radioiodinated interferon-IFNAR complex as disclosed in the references.

Accordingly, in view of the lack of motivation to isolate an interferon IFNAR cross-linked complex, regardless of whether or not the interferon is radioiodinated, the present claims are not obvious over the references of record in the sense of 35 USC 103.

The examiners also asked applicant to comment on why ^{125}I-radioiodinated interferon is necessarily toxic in view of the fact that radioiodinated products are used *in vivo* for diagnostics. It should be understood that while ^{131}I and ^{123}I are commonly used in radiopharmaceuticals, ^{125}I is not. Attached hereto is a copy of page 130 of Volume 16 of the Kirk-Othmer Encyclopedia of Chemical Technology, Fourth Edition, 1995, a copy of which is attached hereto as Appendix A, in which Table 4 shows radioactive nucleotide used in radiopharmaceuticals. Note that ^{125}I is not included. It is known that ^{125}I has a half-life of 59.9 days and a gamma ray intensity which is 74%, while ^{123}I has a half-life of only 13 hours and gamma ray intensity of only 46%. See page B-305 of CRC Handbook of Chemistry and Physics, 69th Edition, 1988-1989, a copy of which is attached hereto as Appendix B. This is why ^{125}I-IFN would be considered toxic and, thus, would not fall in the definition of functional derivative of the present invention.

Claims 1-24 have been rejected under 35 USC 112, second paragraph, as being indefinite in the recitation of "type I IFN biological activity". The examiner states that on page 33 of the specification this term encompasses both agonist and antagonist activity and, as a result, the recitation of "biological activity" is insufficient.

The claims have now been amended to specify that the biological activity for the fragments and variants is agonist activity. This is defined on page 33 of the specification as the ability to bind to a native cell surface receptor and thereby mediate signal production by the receptor. It is the purpose of the fragments or variants to maintain the biological activity of the native interferon and not to create an antagonist. Therefore, the claims now specify that it is the agonist activity that is required. In view of this amendment, it is believed that claims 1 and 24 are no longer indefinite. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully

comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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